UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,516	04/03/2002	Michel G. Bergeron	GGD-31611-PCTUS	5405

22202 7590 08/10/2005

WHYTE HIRSCHBOECK DUDEK S C
555 EAST WELLS STREET
SUITE 1900
MILWAUKEE, WI 53202

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/980,516	Applicant(s) BERGERON ET AL.	
	Examiner Phuong Huynh	Art Unit 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 June 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *three* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: *None*.
   Claim(s) rejected: *1-20*.
   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

S-8

Continuation of 5. Applicant's reply has overcome the following rejection(s): (1) The new matter rejection of claim 10 under 35 U.S.C. 112, first paragraph is hereby withdrawn in view of the amendment to claim 10. (2) The rejection of claims 15-16 under 35 U.S.C. 112, second paragraph is hereby withdrawn in view of the amendment to claims 15-16. (3) The rejection of claims 1-9, 11-16 and 20 under 35 U.S.C. 102(a) as being anticipated by Dufresne et al (Biochimica et Biophysica Acta 1421: 284-294, Oct 1999; PTO 1449) is hereby withdrawn in view of the present application claims priority to canadian application no 2,270,600, which was filed May 3, 1999 and predates the Dufresne reference. (4) The obvious type rejection of claims 1, 10, 12-14, and 17-18 under 35 U.S.C. 103(a) as being unpatentable over Dufresne et al (Biochimica et Biophysica Acta 1421: 284-294, Oct 1999; PTO 1449) in view of Zelphati et al (Antisense Res Dev 3(4): 323-38, 1998; PTO 1449) is hereby withdrawn for the reason that certified copy of the priority document has been received in this National Stage application from the internal Buureau. (5) The obvious type rejection of claims 1, 12 and 19 under 35 U.S.C. 103(a) as being unpatentable over Dufresne et al (Biochimica et Biophysica Acta 1421: 284-294, Oct 1999; PTO 1449) in view of US Pat No 5,773,027 (or record, June 30, 1998; PTO 892) is hereby withdrawn for the same reason of record.

Continuation of 11. does NOT place the application in condition for allowance because:
Claims 1-2 and 10-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (Antiviral Research 33: 11-20, 1996; PTO 892) in view of Catin et al (J Virology 71(3): 1922-1930, March 1997; PTO 892).

Applicants' arguments filed 6/20/05 have been fully considered but are not found persuasive.
Applicants' position is that combining Selvam et al and Cantin et al would change the principle of operation of Selvam et al. Selvam et al teaches the use of anti-CD monocloanl antibody conjugated to the surface of liposomes. Salvam et al use anti-CD4 monoclonal antibodies to bind to CD4 on cells to deliver encapsulted phosphorothioate antisense complementary to the HIV rev region. Cantin et al teaches that HIV-1 and HIV-2 incorporate HLA-DR while budding out the infected cells and suggest that virally aquired host molecule is physically present on the surface of progeny virus. Cantin et al teaches that cellular activation leads to an increase in surface expression of HLA-DR glycoproteins, page 1922, col. 2. The principle of operation fo Sevlam et al involves targeting CD4 which is expressed on the surface of HIV infected cells. Modifying Selvam et al based on Cantin et al's disclosure, as suggested by the Examiner, would result in targeting HLA-DR, which unlike CD4, is expressed on both the surface of activated cells and the HIV virons themselves. This would change the principle of operation of Selvam et al which employs liposomes with anti-CD4 antibodies that bind only to the surface of HIV infected cells. The principles of Selvam et al would additionally be changed because CD4, to which the monoclonal antibody of Selvam et al is directed, is expressed on both resting and activated T cells. In contrast, HLA-DR is not; it is expressed only on activated T cells. There wold be no reasonble expectation of success that coupling an HLA-DR protein binding ligand to a lipid-containng vesicle would result in an effective formulatio to bind HLA-DR.

In contrast to applicant's assertion that HLA-DR is expressed only on activated T cells and not on resting T cells, Cantin et al teach HLA-DR is expressed consitutively on resting T cell and monocyte-derived macrophage and HLA-DR surface expression increases following cellular activation, i.e. HIV infection (see page 1922, col. 2, in particular). In contrast to applicant' argument that there is no motivation of success, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

In this case, the teachings of Selvam et al pertaining to the advantage of targeting HIV infected cells using anti-CD4 coupled to liposome and the teachings of Cantin indicating HLA-DR is a natural ligand for CD4 and HIV infected cells has an increased expression of HLA-DR would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem of targeting HIV infected cells in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

Claims 3-9 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (Antiviral Research 33: 11-20, 1996; PTO 892) in view of Catin et al (J Virology 71(3): 1922-1930, March 1997; PTO 892) as applied to claims 1-2 and 10-18 and further in view of US Pat No 5,773,027 (or record, June 30, 1998; PTO 892).

Applicants' arguments filed 6/20/05 have been fully considered but are not found persuasive.
Applicants' position is that neither the '027 patent or the Harlow et al reference cures the deficiences in the teachings of Selvam et al and Cantin et al. The '027 patent teaches liposmes for the treatment of viral diseases and more particularly for the treatment of infections caused by HIV and CMV. The '027 patent fails to provide any information about a ligand capable of binding to HLA-DR protein. Harlow et al also fails to teach or suggest anything about a ligand capable of binding to a HLA-DR protein, as recited in claim 1.

In response, the teachings of the Selvem and Cantin et al have been discussed supra and is incorporated here by reference. In response to applicant's argument that neither the '027 patent or the Harlow et al teach ligand capable of binding to HLA-DR, Cantin et al teach CD4 is a natural ligand for HLA-DR (see apge 1927, col. 1, in particular).

The combined teachings of Selvam et al and Cantin et al have been discussed supra.
The invention in claim 3 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10: 1 and 1:1 wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length.

The invention in claim 4 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine.
The invention in claim 5 differs from the teachings of the reference only in that the formulation wherein the liposome wherein the

polyethyleneglycol has a molecular weight between 500 and 5000 daltons.

The invention in claim 6 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio is 10: 3.

The invention in claim 7 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanolamine polyethyleneglycol in a molar ratio of 10:3:0.1-3. The invention in claim 8 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3 or disterearolyphosphatidylcholine: distearoylphosphatidycholine: distearoylphosphatidylglycerol in a molar ratio of 10:3.

The invention in claim 9 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol: dipalmitoyphophatidylethanolmine-polyethyleneglycerol in a molar ratio of 10:3:0.33 or dipalmitoylphosphatidylcholine: dipalmitolyphosphatidycholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3:0.83.

The invention in claim 19 differs from the teachings of the reference only in that the formulation which comprises a drug wherein the drug is selected from the group consisting of AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin.

The '027 patent teaches a formulation for treatment of viral disease such as HIV which comprises a lipid vesicle or liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (palimitoyl which is 16 carbon or stearoyl which is 18 carbon in length) (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The reference formulation wherein the lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of '027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine (DPPC) and diacylphosphatidylglycerol (DSPG) in a molar ratio of 10:3 (See col. 3, liens 46-47, in particular) and a formulation wherein the lipid component comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10 to 3 to 1.45 which is between the claimed 0.1-3 (See col. 5, lines 46-47, in particular). The reference formulation further encapsulated a drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the liposome that coupled to a ligand capable of binding to a HLA-DR protein as taught by Selvam et al and Catin et al for the liposome with encapsulated drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for targeting to HIV as taught by the '027 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because not all the liposomal formulations have shown efficient drug encapsulation and drug retention and sterically stabilized liposomes have higher efficiency of drug encapsulation and drug retention by reduced leakage of entrapped drug as taught by the '027 patent (see col. 3, line 51 bridging col. 4, lines 1-27, in particular). Further, targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases as taught by the '027 patent (See col. 2, lines 25-31, col. 9, lines 7-12, in particular). HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin et al (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular).

Claims 1, 11 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (Antiviral Research 33: 11-20, 1996; PTO 892) in view of Catin et al (J Virology 71(3): 1922-1930, March 1997; PTO 1449) and Harlow et al (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629).

Applicants' arguments filed 6/20/05 have been fully considered but are not found persuasive.
Applicants' position is that neither the '027 patent or the Harlow et al reference cures the deficiences in the teachings of Selvam et al and Cantin et al. The '027 patent teaches liposmes for the treatment of viral diseases and more particularly for the treatment of infections caused by HIV and CMV. The '027 patent fails to provide any information about a ligand capable of binding to HLA-DR protein. Harlow et al also fails to teach or suggest anything about a ligand capable of binding to a HLA-DR protein, as recited in claim 1.

In response, the teachings of the Selvem and Cantin et al have been discussed supra and is incorporated here by reference. In response to applicant's argument that neither the '027 patent or the Harlow et al teach ligand capable of binding to HLA-DR, Cantin et al teach CD4

is a natural ligand for HLA-DR (see apge 1927, col. 1, in particular).
The combined teachings of Selvam et al and Cantin et al have been discussed supra.

The invention in claim 11 differs from the teachings of the reference only in that the formulation wherein the ligand is an antibody fragment.
The invention in claim 20 differs from the teachings of the reference only in that the formulation wherein the ligand is an anti-Fab' fragment directed against HLA-DR.

Catin et al teach HIV acquired host protein such as HLA-DR, ICAM-1 (CD54), CD55 (DAF), CD59, CD63 and CD71 (see page 1922, col. 1, in particular). Catin et al teach antibody to HLA-DR or anti-LFA-1 (CD11a) inhibit HIV infection since HIV virus acquired host cellular protein on the surface of the progeny virus (see page 1922, col. 1, in particular). Catin et al teach CD4 molecule is the primary cell surface receptor for HIV-1 (page 1922, col. 2, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 (see page 1922, col. 2, in particular). The reference HLA-DR protein is expressed in lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages (see page 1922, col. 2, in particular).
Harlow et al teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular).

Harlow et al further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make Fab fragment thereof as taught by Harlow et al using the anti-HLA-DR as taught by Catin et al and then substituting the anti-CD4 in the anti-CD4 coupled liposome as taught by Selvam et al for a formulation which comprises a ligand capable of binding to a HLA-DR protein such as anti-HLA-DR Fab fragment being coupled to a lipid-comprising vesicle as taught by Selvam et al, Catin et al and Harlow at al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody and antibody fragment because Harlow et al teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular). One having ordinary skill in the art would have been motivated to do this because HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular).

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT 182 1644